PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/55	A1	(11) International Publication Number: WO 96/32947
		(43) International Publication Date: 24 October 1996 (24.10.96)

(21) International Application Number: PCT/US96/05379

(22) International Filing Date: 18 April 1996 (18.04.96)

(30) Priority Data:
08/422,202 21 April 1995 (21.04.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/422,202 (CON)
Filed on 21 April 1995 (21.04.95)

(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: RASMUSSEN, Kurt [US/US]; 9735 Logan Lane, Fishers, IN 46038 (US).

(74) Agents: VORNDRAN-JONES, MaCharri et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD FOR TREATING NICOTINE WITHDRAWAL

(57) Abstract

The invention provides a method for treating a condition resulting from the cessation and withdrawal from the use of nicotine comprising administering an effective amount of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

METHOD FOR TREATING NICOTINE WITHDRAWAL

This invention provides a method for using 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, for the treatment nicotine withdrawal and alleviation of the craving for a tobacco product.

Over 25 years ago, the Surgeon General issued a report linking cigarette smoking to cancer, heart disease, respiratory disease and other conditions. Despite such information being available to the public, cigarette smoking remains a significant preventable cause of death in the United States and other developed countries.

Benowitz, *N. Eng. J. Med.* 319:20, 1318-1330 (November 17, 1988) notes that many people who smoke cigarettes would like to quit but cannot because they are addicted to the psychoactive drug that is the dependence-producing constituent of tobacco, nicotine.

Benowitz notes that nicotine may also contribute to the diseases for which smoking is a risk factor, particularly heart disease. Nicotine is also present in other tobacco products that are smoked or chewed, which are also addictive and associated with heart, lung, and other serious disease states.

Pharmacologic therapies are known to help those addicted to nicotine. Receptor antagonists such as mecamylamine have been used to reduce the satisfaction obtained from tobacco use. Unfortunately, this therapy has the short term effect of increasing tobacco consumption to overcome the receptor antagonism as well as other undesirable side effects.

Non-receptor antagonists have also been used, such as clonidine to reduce the craving for tobacco and other tobacco related withdrawal symptoms. According to Benowitz,

one recent study using clonidine treatment for six weeks was found to be more effective than placebo, but only for women.

Benowitz reports that the most effective treatment thus far has been nicotine substitution therapy, using nicotine gum, or other nicotine forms to slowly wean individuals from the addiction to nicotine and the tobacco products containing nicotine. Unfortunately, the nicotine substitution therapy involves the administration of the psychoactive constituent of tobacco which has been identified as a contributor to the diseases associated with smoking. Nicotine substitution must be tapered; frequently leading to nicotine withdrawal and subsequent relapse to smoking. There is a need for a therapy having a desirable side effect profile, to relieve nicotine withdrawal symptoms, including the long term cravings for nicotine.

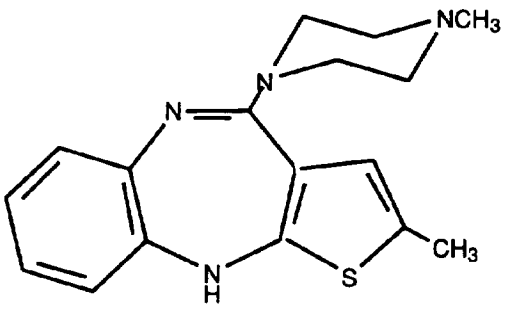
It is known that the compound 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine can provide antipsychotic activity and is less likely to induce extrapyramidal symptoms. Surprisingly, Applicant has discovered that 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine can be useful for treating a condition which is a response produced by cessation and withdrawal from the use of nicotine. The compound 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine is known and described in U.S. Patent No. 5,229,382, herein incorporated by reference in its entirety.

Summary Of The Invention

The presently claimed invention provides a method for treating a condition which is a response produced by cessation and withdrawal from the use of nicotine, comprising administering an effective amount of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine or a pharmaceutically acceptable salt thereof to a patient in need of such treatment.

Detailed Description of the Invention

The 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine compound is of the formula



(I)

or an acid addition salt thereof. The free base of formula (I) is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.

Substantially pure Form II olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307

4.2294
4.141
3.9873

d
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03

4.7158	6.80
4.4787	14.72
4.3307	1.48
d	I/I_1
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper $K\alpha$ radiation source of wavelength, $\lambda = 1 \cdot 541$Å.

As used herein "substantially pure" refers to Form II associated with less than about 5% Form I, preferably less than about 2% Form I, and more preferably less than about 1% Form I. Further, "substantially pure" Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water. In particular, "substantially pure" Form II should contain less than about 0.05% content of acetonitrile, more preferably, less than about 0.005% content

of acetonitrile. Additionally, the polymorph of the invention should contain less than 0.5% of associated water.

The term "Form I" shall refer to the polymorph obtainable using the teachings of the '382 patent. x-ray powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873

d
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739

2.8102
2.7217
2.6432
2.6007

A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48
d	I/I_1
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34

3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper $K\alpha$ radiation source of wavelength, $\lambda = 1 \cdot 541 Å$.

As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

As used herein, the term "nicotine withdrawal" or "cessation and withdrawal from the use of nicotine" shall refer to a condition resulting from discontinued consumption of tobacco products and consequently, a result of discontinued consumption of nicotine. Such nicotine withdrawal conditions are characterized in the DSM-IV-R. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The DSM-IV-R was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic catagories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress.

Therefore, the term "cessation and withdrawal from the use of nicotine" shall include, but is not limited to the following conditions characterized in the DSM-IV-R: Nicotine Withdrawal; Nicotine-Related Disorder Not otherwise

Specified; Nicotine Dependence, with physiological dependence; Nicotine Dependence, without physiological dependence; Nicotine Dependence, Early Full Remission; Nicotine Dependence, Early Partial Remission; Nicotine Dependence, Sustained Full Remission; and Nicotine Dependence, Sustained Partial Remission; Nicotine Dependence, On Agonist Therapy.

The discontinued use of tobacco products, all of which contain nicotine, results in the onset of nicotine withdrawal syndrome. Individuals typically suffer the symptoms of nicotine withdrawal resulting from the discontinued use of tobacco in any form, including, but not limited to smoking of cigarette, cigar, or pipe tobacco, or the chewing of snuff or chewing tobacco. The cessation of nicotine use or reduction in the amount of nicotine use, is often followed within 24 hours by dysphoric, depressed mood; insomnia; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain. These symptoms often cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The present invention is most preferably used to alleviate symptoms attributed to nicotine withdrawal when such symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

The method of the present invention is preferably administered in connection with and/or subsequent to an educational and/or behavioral modification program to ensure continued abstinence from tobacco products. The method of the present invention is also highly beneficial to such programs by alleviating the suffering experienced from the nicotine withdrawal over the course of such programs. Therefore, the programs can be more effective by focusing on educational and behavioral modification goals, further reducing the incidence of program non-completion.

The results of pharmacological studies show that 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-

b][1,5]benzodiazepine has muscarinic cholinergic receptor activity. The compound is active at the dopamine D-1 and D-2 receptors as indicated by an IC50 of less than 1 uM in the 3H-SCH233390 (Billard, et al. Life Sciences **35**:1885 (1984)) and the 3H spiperone (Seeman et al Nature **216**:717 (1976)) binding assays respectively. Further, olanzapine is active at the 5-HT-2 receptor and 5-HT1C receptor. The complex pharmacological profile of the compound provides a medicament which can be useful for the treatment of a condition resulting from cessation and withdrawal from the use of nicotine.

In vivo animal and clinical observations support that 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine has a complex muscarinic receptor subtype profile. For example, rats exposed to an overdose of the compound surprisingly exhibited significant salivation. Further, clinical subjects experienced pupilary constriction rather than the expected pupilary dialation.

The usefulness of the compound for treating a condition resulting from cessation and withdrawal from the use of nicotine can be supported by the following studies as described.

I. Auditory Startle Response.

Male Long Evans rats (Harlan Sprague Dawley) are individually housed in a controlled environment on a 12 hour light-dark cycle. The rats are given free access to food and water. All treatment groups contain from 8 to 10 rats.

The rats are anesthetized with halothane and Alzet osmotic minipumps (Alza Corporation, Palo Alto, California) are implanted subcutaneously. Nicotine ditartrate is dissolved in physiological saline. Pumps are filled with nicotine ditartrate (6 mg/kg base/day) or the appropriate vehicle. Twelve days following implantation of pumps, rats are anesthetized with halothane and the pumps are removed.

The auditory Startle Response is observed.

The sensory motor reactions [auditory startle response (peak amplitude, V_{max})] of individual rats are recorded using San Diego Instruments startle chambers (San Diego, Calif.). Startle sessions consist of a 5 minute adaptation period at background noise level of 70 +/- 2dBA immediately followed by 25 presentations of auditory stimuli (120 +/-3 dBA noise, 50 ms duration) presented at 8 second intervals. Peak startle amplitudes are averaged for all 25 presentations of stimuli for each session. Auditory startle responding is evaluated daily at 24 hour intervals on days 1-4 following nicotine withdrawal.

The 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine compound is administed at six doses about 60 minutes before startle testing each day.

The compound 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine can be used for the methods of this invention, both in its free base and acid addition salt forms. The acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those of inorganic acids, for example hydrochloric, hydrobromic, nitric, sulfuric or phosphoric acids, or of organic acids, such as organic carboxylic acids, for example glycollic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric or lactic acid, or organic sulfonic acids for example methane sulfonic, ethane sulfonic, 2-hydroxyethane sulfonic, toluene-p-sulfonic or naphthalene-2-sulfonic acid.

The compound 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine can be prepared using the methods taught in the '382 patent *supra*.

It will be appreciated that the compound of formula (I) may be isolated per se or may be converted to an acid addition salt using conventional methods.

The compound has an IC_{50} of less than 1 mM in the ^{3}H-QNB binding assay described by Yamamura, HI and

Snyder, SH in Proc.Nat.Acad.Sci. USA 71 1725 (1974) indicating that it has muscarinic-cholinergic activity.

The 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine compound is effective over a wide dosage range, the actual dose administered being dependent on the condition being treated. For example, in the treatment of adult humans, dosages of from about 0.25 to 50 mg, preferably from 1 to 30 mg, and most preferably 1 to 20 mg per day may be used. A once a day dosage is normally sufficient, although divided doses may be administered. For treatment of a condition resulting from cessation and withdrawal from the use of nicotine, a dose range of from 1 to 30 mg, preferably 1 to 20 mg per day is suitable. Radiolabelled 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine, can be detected in the saliva and thus the compound can potentially be monitored in patients to assess compliance.

A preferred formulation of the invention is a solid oral formulation comprising from about 1 to about 20 mg or 1 to 10 mg of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine as an effective amount of the active ingredient.

Most preferably, the solid oral formulation is contained in packaging materials which protect the formulation from moisture and light. For example, suitable packaging materials include amber colored high density polyethylene bottles, amber colored glass bottles, and other containers made of a material which inhibits the passage of light. Most preferably, the packaging will include a desiccant pack. The container may be sealed with an aluminum foil blister to provide the desired protection and maintain product stability.

The 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine compound will normally be administered orally or by injection and, for this purpose, it is usually employed in the form of a pharmaceutical composition.

Accordingly, pharmaceutical compositions comprising 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, as active ingredient associated with a pharmaceutically acceptable carrier may be prepared. In making the compositions of the invention conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. The active ingredient can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxy-benzoate, talc, magnesium stearate or mineral oil. The compositions of the invention may, if desired, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient. For example, one such preferred quick release formulation is described in U.S. Patent Nos. 5,079,018, 5,039,540, 4,305,502, 4,758,598, and 4,371,516, hereby incorporated by reference. Such formulation most preferably comprises 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, water, hydrolyzed gelatin, and mannitol.

Depending on the method of administration, the compositions for the treatment of central nervous system conditions may be formulated as tablets, capsules, injection solutions for parenteral use, gel or suspension for transdermal delivery, suspensions or elixirs for oral use or suppositories. Preferably the compositions are formulated in a unit dosage form, each dosage containing from 0.25 to 100 mg, more usually 1 to 30 mg, of the active

ingredient. When a sustained release formulation is desired, the unit dosage form may contain from 0.25 to 200 mg of the active ingredient. A preferred formulation of the invention is a capsule or tablet comprising 0.25 to 75 mg or 1 to 30 mg of active ingredient together with a pharmaceutically acceptable carrier therefor. A further preferred formulation is an injection which in unit dosage form comprises 0.25 to 30 mg or 1 to 30 mg of active ingredient together with a pharmaceutically acceptable diluent therefor.

The materials for the present invention can be purchased or prepared by a variety of procedures well known to those of ordinary skill in the art. The 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine compound can be prepared as described by Chakrabarti in U.S. Patent No 5,229,382 ('382), herein incorporated by reference in its entirety. It is most desirable to prepare a rapidly dissolving formulation comprising 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine. Such 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine may be prepared using the techniques described herein by the Preparation section herein *infra*.

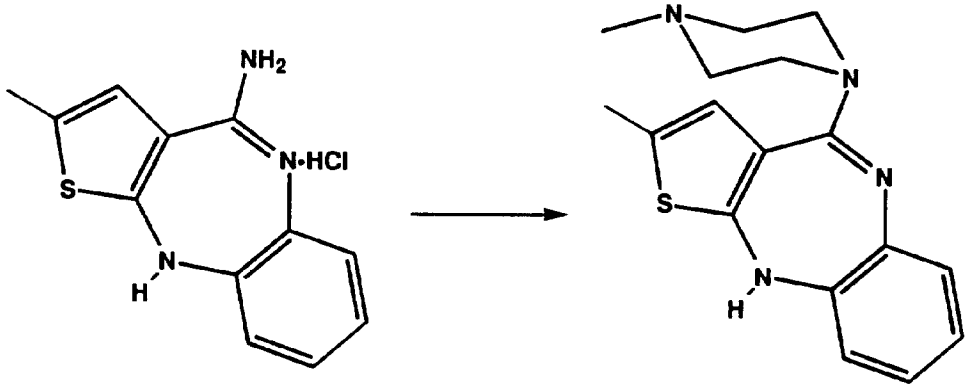
As used herein mixing steps may be accomplished using common agitation methods such as stirring, shaking, and the like. As used herein the phrase "producing crystalline product from the mixture" shall refer to crystallization from the stated mixture of compound and solvent. Further, the artisan recognizes that crystallization processes may include seeding, chilling, scratching the glass of the reaction vessel, and other such common techniques.

Compound characterization methods include, for example, x-ray powder pattern analysis, thermogravimetric analysis (TGA), differential scanning calorimetery (DSC), titrametric analysis for water, and H^1-NMR analysis for solvent content.

The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

Preparation 1

Technical Grade olanzapine



Intermediate 1

In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical)	:	6 volumes
Intermediate 1	:	75 g
N-Methylpiperazine (reagent)	:	6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the '382 patent.

A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until ≤ 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction

was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Form II

A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L) . The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.

Yield: 197 g.

The process described above for preparing Form II provides a pharmaceutically elegant product having potency $\geq$ 97%, total related substances $<$ 0.5% and an isolated yield of $>$ 73%.

EXAMPLE 1

A portion of the hydroxypropyl cellulose was dissolved in purified water to form a solution for granulation. The remaining hydroxypropyl cellulose (total of 4.0% w/w final tablet weight), which was an extra fine grade, was combined with the 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine (1.18% w/w), lactose (79.32% w/w) and a portion of the crospovidone (5% w/w) in a high shear granulator. All ingredients were security sieved prior to addition and dry blended in the granulator. This mixture was then granulated with the hydroxypropyl cellulose

solution in the high shear granulator. The granulation was wet sized using standard methods. The wet granulation was then dried in a fluidized bed dryer and sized. The material was then added to a tumble bin mixer.

The running powders consisting of microcrystalline cellulose (granular) (10% w/w), magnesium stearate (0.5% w/w), and the remainder of the crospovidone were added to the sized granulation. The mixture was blended and compressed with the appropriate tooling on tablet compression equipment.

Subcoating:

Hydroxypropyl methylcellulose (10% w/w) was mixed with purified water to form a solution. Core tablets were divided into approximately equal sections and spray coated with the hydroxypropyl methylcellulose solution . The operation was performed in a perforated coating pan.

Coating of Core Tablets:

Color Mixture White (hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide) was mixed with purified water to form the coating suspension. Subcoated tablets were divided into approximately equal sections and spray coated with the coating suspension described above. The operation was performed in a perforated coating pan.

The coated tablets were lightly dusted with carnauba wax and imprinted with appropriate identification.

EXAMPLE 2

The process substantially as described above in Example 1 was repeated using the following ingredients to provide pharmaceutically elegant tablet formulations containing 1, 2.5, 5, 7.5, and 10 mg 2-methyl-4-(4-methyl-

1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, respectively, per tablet:

1 mg 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine per tablet:

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	1.0
Other Ingredients	
Lactose	67.43
Hydroxypropyl Cellulose	3.40
Crospovidone	4.25
Microcrystalline Cellulose	8.50
Magnesium Stearate	0.42
Subcoating	
Hydroxypropyl Methylcellulose	1.70
Coating	
Color Mixture White	3.47
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine 2.5 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	2.5
Other Ingredients	
Lactose	102.15
Hydroxypropyl Cellulose	5.20
Crospovidone	6.50
Microcrystalline Cellulose	13.00
Magnesium Stearate	0.65

Subcoating	
Hydroxypropyl Methylcellulose	2.60
Coating	
Color Mixture White	5.30
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine 5.0 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	5.00
Other Ingredients	
Lactose	156.00
Hydroxypropyl Cellulose	8.00
Crospovidone	10.00
Microcrystalline Cellulose	20.00
Magnesium Stearate	1.00
Subcoating	
Hydroxypropyl Methylcellulose	4.00
Coating	
Color Mixture White	8.16
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

5

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine 7.5 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	7.50

Other Ingredients	
Lactose	234.00
Hydroxypropyl Cellulose	12.00
Crospovidone	15.00
Microcrystalline Cellulose	30.00
Magnesium Stearate	1.50
Subcoating	
Hydroxypropyl Methylcellulose	6.00
Coating	
Color Mixture White	12.24
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine 10.0 mg Tablets

Names of Ingredients	Quantity (mg/tablet)
Active Ingredient	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	10.00
Other Ingredients	
Lactose	312.00
Hydroxypropyl Cellulose	16.00
Crospovidone	20.00
Microcrystalline Cellulose	40.00
Magnesium Stearate	2.00
Subcoating	
Hydroxypropyl Methylcellulose	8.00
Coating	
Color Mixture White	16.32
Polishing	
Carnauba Wax	trace
Imprinting	
Edible Blue Ink	trace

EXAMPLE 4

Pulvule Formulation

A pulvule formulation is prepared by blending the active with silicone starch, and filling it into hard gelatin capsules.

	Per 300 mg capsule
Compound of the invention	30.0 mg
Silicone	2.9 mg
Starch flowable	267.1 mg

EXAMPLE 5

Tablet Formulation

A tablet formulation is made by granulating the active with appropriate diluent, lubricant, disintegrant and binder and compressing

Compound of the invention	10.0 mg
Magnesium stearate	0.9 mg
Microcrystalline cellulose	75.0 mg
Povidone	15.0 mg
Starch, directly compressible	204.1 mg

EXAMPLE 6

Aqueous Injection Formulation

An aqueous injection of active is prepared as a freeze-dried plug, for reconstitution in a suitable, sterile diluent before use (to a total volume of 10 ml).

Compound of the invention is contacted with Mannitol N Hydrochloric acid and/or N sodium hydroxide to adjust pH to 5-5.5.

Compound of the invention	20.0 mg
Mannitol	20.0 mg
N Hydrochloric acid and/or N sodium hydroxide to adjust pH to 5-5.5.	

EXAMPLE 7

Controlled Release IM Formulation

A controlled release injection for intramuscular injection is formed from a sterile suspension of micronised active in an oleaginous vehicle.

Compound of the invention	50.0 mg
Aluminium stearate	0.04 mg
Sesame oil	2 ml

EXAMPLE 8

Capsule Formulation

A formulation is prepared by blending the active with silicone starch and starch, and filling it into hard gelatine capsules.

	Per 300 mg capsule
Compound of the invention	2.5 mg
Starch flowable with 0.96% silicone 220	222.5 mg
Starch flowable	75.0 mg

Example 9

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine Granules

The granules were produced by blending the mannitol and Hydroxymethyl propyl cellulose in a high shear mixer; granulating with the aqueous suspension of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine and polysorbate 20; wet sized and subsequently dried in a fluid bed dryer. These are dry sized and reblended prior to packaging.

1a. 250mg Sachets

INGREDIENT	MG/SACHET
Active	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	2.50
Other Ingredients	
Mannitol	234.97
Hydroxypropyl methyl cellulose 3cps	12.50
Polysorbate 20	0.028

1b. 750mg Sachets

INGREDIENT	MG/SACHET
Active	
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine	7.50
Other Ingredients	
Mannitol	704.93
Hydroxypropyl methyl cellulose 3cps	37.49
Polysorbate 20	0.08

1c. 1000mg Sachets

INGREDIENT	MG/SACHET
Active	

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine	10.0
Other Ingredients	
Mannitol	939.90
Hydroxypropyl methyl cellulose 3cps	49.99
Polysorbate 20	0.11

Such granules are most preferably contacted with an acidic medium if a suspension or solution is desired.

We Claim:

1. A method for treating a condition resulting from the cessation and withdrawal the use of nicotine comprising administering to a mammal in need of such treatment, an effective amount 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine, or a pharmaceutically acceptable salt thereof.

2. A method of **Claim 1** wherein the nicotine use is the smoking of tobacco.

3. A method of **Claim 2** wherein the nicotine use is the smoking of cigarettes.

4. A method of **Claim 1** wherein the condition is selected from the group consisting of Nicotine Withdrawal; Nicotine-Related Disorder Not otherwise Specified; Nicotine Dependence, with physiological dependence; Nicotine Dependence, without physiological dependence; Nicotine Dependence, Early Full Remission; Nicotine Dependence, Early Partial Remission; Nicotine Dependence, Sustained Full Remission; Nicotine Dependence, Sustained Partial Remission; and Nicotine Dependence, On Agonist Therapy.

5. A method of **Claim 4** wherein the condition is Nicotine Withdrawal.

6. A method of **Claim 1** whererin the nicotine use is the chewing of snuff.

7. A method of **Claim 1** wherein 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine is substantially pure Form II 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5] benzodiazepine having a typical X-ray powder diffraction pattern substantially as

follows, using a Sieman's D5000 diffractometer wherein d represents the interplanar spacing:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
d
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

8. A method of **Claim 7** wherein the condition is selected from the group consisting of Nicotine Withdrawal; Nicotine-Related Disorder Not otherwise Specified; Nicotine Dependence, with physiological dependence; Nicotine Dependence, without physiological dependence; Nicotine Dependence, Early Full Remission; Nicotine Dependence, Early Partial Remission; Nicotine Dependence, Sustained Full Remission; Nicotine Dependence, Sustained Partial Remission; and Nicotine Dependence, On Agonist Therapy.

9. A method of **Claim 8** wherein the condition is selected from the group consisting of Nicotine Dependence, with physiological dependence; Nicotine Dependence, Early Full Remission; Nicotine Dependence, Early Partial Remission; Nicotine Dependence, Sustained Full Remission; Nicotine Dependence, Sustained Partial Remission; and Nicotine Dependence, On Agonist Therapy.

10. A method of **Claim 8** wherein the condition is selected from the group consisting of Nicotine Withdrawal; Nicotine-Related Disorder Not otherwise Specified; Nicotine Dependence, with physiological dependence; Nicotine Dependence, Early Full Remission; and Nicotine Dependence, Early Partial Remission.

11. A method of **Claim 10** wherein the condition is Nicotine Withdrawal.

12. A method of **Claim 1** wherein the effective amount is from about 1 mg to about 20 mg per day.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05379

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/55
US CL :514/220, 813
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/220, 813

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, BIOSIS, EMBASE, USPATFULL, WPIDS- THERAPEUTIC USES FOR COMPOUNDS HEREIN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	CORBETT, et al., Antipsychotic agents antagonize non-competitive N-methyl-D-aspartate antagonist-induced behaviors. Psychopharmacology. 01 July 1995, Vol. 120, Number 1, pages 67-74, see entire document.	1-12
Y	US 5,321,012 A (MAYER) 14 June 1994, see entire document.	1-12
A	US 5,229,382 A (CHAKRABARTI) 20 July 1993, see entire document.	1-12
A	Database Hcaplus on STN, American Chemical Society, AN 1993:662437, ANDO, et al. " Dependence Study On LY170053 In Rhesus Monkeys And Rats," abstract, Jitchuken Zenrinsho Kenkyuho (Japan) 1993.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
02 AUGUST 1996	27 AUG 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer M. MOEZIE
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*